Remarks

Claims 33-53 were pending in the subject application. By this Amendment, claims 33, 45, 49, and 50 have been amended, claims 34-36, 42-44, 46-48, and 51-53 have been cancelled, and claims 37-41, 45, and 49 have been withdrawn. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 33 and 50 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 for the subject application. Also submitted herewith is an Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

Claims 33 and 50 are product claims. Claims 37-41, 45, and 49 are process claims for making or using the product, within the meaning of MPEP § 821.04. Therefore, pursuant to MPEP § 821.04, upon an indication of an allowable product claim, the applicants respectfully request that claims 37-41, 45, and 49 be rejoined and examined in the subject application.

By this Amendment, the applicants have amended claims 33 and 50 to recite that the immunogenic composition comprises nanospheres comprising plasmid DNA coacervated with chitosan, wherein the plasmid DNA encode the following nine respiratory syncytial virus (RSV) antigens: M2, F, G, M, SH, NS1, NS2, N, and P. Support for this amendment can be found, for example, at page 4, lines 3-7, of the subject specification.

Claims 33, 34, and 36 have been rejected under 35 U.S.C. §103(a) as being obvious over Connors *et al.* (*J. Virol*, 1991, 65(3):1634-1637) in view of Li *et al.* (*J. Exp. Med.*, 1998, 188(4):681-688) and Li *et al.* (*Virology*, 2000, 269:54-65), and further in view of Leong (*J. Controlled Release*, 1998, 53:183-193). Claim 35 has been rejected under 35 U.S.C. §103(a) as being obvious over Connors *et al.* in view of Li *et al.* (1998) and Li *et al.* (2000), and further in view of Leong. Claims 50-53 have been rejected under 35 U.S.C. §103(a) as being obvious over Connors *et al.* in view of Li *et al.* (1998) and Li *et al.* (2000) and Leong, and further in view of Illum (WO 90/09780) and

Rolland *et al.* (U.S. 6,184,037). The applicants respectfully submit that the cited references do not teach or suggest the subject invention with any reasonable expectation of success. As indicated above, the applicants have cancelled claims 34 and 36, and amended claims 33 and 50 to recite that the immunogenic composition comprises nanospheres comprising plasmid DNA coacervated with chitosan, wherein the plasmid DNA encode the following nine RSV antigens: M2, F, G, M, SH, NS1, NS2, N, and P.

As the Examiner is aware, any rejection of a claim for obviousness must include a finding that one of ordinary skill in the art at the time the invention was made would have reasonably expected the claimed invention to work. *Hodosh v. Block Drug Co.*, 786 F2d 1136 (Fed Cir 1986); *In re Merck & Co., Inc.*, 800 F.2d 1091; 231 USPQ 375 (Fed. Cir. 1986). The applicants respectfully disagree with the Examiner's conclusion that "the cumulative teachings of these references both suggest the claimed inventions, and provide a reasonable expectation of success in the use of the compositions to induce an immune response against RSV." The applicants respectfully submit that the cited references would not impart any reasonable expectation of success to one of ordinary skill in the art. Submitted with the Information Disclosure Statement that accompanies this Amendment are the following publications for the Examiner's consideration: Ward, B.J., "Vaccine adverse effects in the new millennium: is there reason for concern?" *Bulletin of the World Health Organization*, 2000, 78(2):205-215; Doolan D. L. *et al.*, "Utilization of genomic sequence information to develop malaria vaccines", *Journal of Experimental Biology*, 2003, 206:3789-3802; Muthumani K. *et al.*, "Issues for improving multiplasmid DNA vaccines for HIV-1", *Vaccine*, 20(2002):1999-2003; Moorthy V. S. *et al.*, "Malaria vaccine developments", *The Lancet*, 363:150-156; and Dumonteil E. *et al.*, "DNA vaccines induce partial protection against *Leishmania mexicana*", *Vaccine*, 2003, 21(2003):22161-2168. These publications show that the immune response to a composition employing a combination or "cocktail" of antigens cannot be predictably determined from responses obtained from the same antigens individually.

Even in situations where each component antigen of an antigen combination has been evaluated *in vivo*, how to combine multiple antigens without interference or competition remains an important issue. Combined antigens can have unpredictable effects upon each other (interaction), perhaps magnifying the effect of one antigen, while blocking the effect of another. Concerns about

negative antigen interactions have been expressed in the scientific literature for some time (see, for example, the abstract of Muthamani *et al.*; page 2166, second column, lines 30-54, of Dumonteil *et al.*; and page 153, last paragraph, of Moorthy *et al.*). As indicated in the Ward publication, multivalent vaccines can have great advantages. However, they may also

> induce immune responses which are quantitatively and qualitatively different from those engendered by single antigen or single organism products. It is now well established that simultaneous administration of antigens A+B can alter the magnitude and patter of immune response to both A and B. Whether or not the altered immune responses generated by these vaccines are equally efficacious, durable and safe will have to be carefully monitored despite, in some cases, our many years of experience with the individual component antigens. (page 209, second column, 9-19, of the Ward publication, emphasis added)

The Doolan *et al.* publication indicates that "how best to mimic the complexity of multi-antigenic whole organism vaccines by subunit vaccination is not obvious ... A basic conundrum is that adding antigens to a multi-antigen cocktail incrementally reduces the dose of each component and thus may reduce component immunogenicity to the point where protection is lost" (pages 3798-3799, bridging paragraph, emphasis added). Clearly, an additive effect, where 1+1+1 equals 3, does not predictably occur. Indeed, the risk of losing immunogenicity exists every time an antigen is added to the antigen cocktail. The immunogenic composition, as currently claimed, includes plasmid DNA encoding nine RSV antigens. Extrapolation of the results achieved in the cited references to the combination of antigens recited in the claims is not appropriate.

None of the cited references, alone or in combination, establish a reasonable expectation of success in combining the references to arrive at the invention. The Conners *et al.* publication, which is relied upon as the primary reference in each of the foregoing rejections under 35 U.S.C. §103(a), describes experiments evaluating whether nine vaccinia virus-RSV recombinants individually encoding nine RSV proteins are able to induce resistance to RSV challenge. The Office Action cites the Conners *et al.* publication for teaching that each of the tested RSV proteins is capable of inducing an immune response against RSV. However, the cited reference must be taken into consideration as a whole. For example, at page 1635, second column, Conners *et al.* indicate that previous studies identified F and G glycoproteins as the major mediators of resistance to RSV infection with RSV, with the N protein providing partial protection. Further, Conners *et al.* also state that "importantly,

the other RSV proteins (SH, M, P, 1B, and 1C) failed to induce resistance under the experimental conditions used." Thus, Conners *et al.* conclude that "the major antigens to be included in an RSV vaccine are the F and G glycoproteins, which efficiently stimulate neutralizing antibodies", and "RSV antigens need only contain the F and G glycoproteins, because the immunity conferred by the other proteins is less effective and appears to wane rapidly with time" (see 1636, second column, and abstract of Conners *et al.*).

The Office Action relies on the Li *et al.* publications for teaching that the use of plasmid DNA vaccines encoding viral antigens leads to an improved immune response compared to those seen with other vaccines, and a response comparable to that observed with natural RSV infection can be achieved with plasmid vaccines encoding RSV F and G antigens, individually. The Leong *et al.* publication describes coacervating DNA with chitosan to form DNA-chitosan nanospheres capable of expressing β-gal in the muscle of BALB/c mice, and indicates that the nanospheres might be attractive vehicles for DNA vaccine applications. The Illum reference is relied upon by the Office Action for teaching that chitosan particles comprising RSV vaccines may be nasally administered, and the Illum and Rolland references are relied upon in the Office Action for teaching that chitosan microparticles encapsulating DNA may be administered as an inhalant.

Here, it is only the applicants' disclosure that provides the teaching that coacervates of chitosan and plasmid DNA encoding nine RSV antigens can be synthesized and delivered to a host, wherein the antigen-encoding DNA is expressed at sufficient levels within the host's cells to achieve immunogenicity. As indicated at page 14, lines 12-13, of the specification, and Figures 1A, 1B, and 6A, expression of all nine RSV antigens was confirmed using RT-PCR and immunoblot analysis. Synthesis of nanospheres that successfully express the plasmid DNA encoding each of the nine recited antigens is dependent on several interrelated factors including, for example, plasmid concentration, chitosan concentration, the ratio of plasmid to chitosan, the molecular weight of chitosan, temperature, mode of mixing, pH, and the size and surface charge of the particles. The cited references do not establish that nanospheres comprising coacervated chitosan and plasmid DNA encoding nine RSV antigens can be used to deliver and express each antigen resulting in immunogenicity.

The applicants respectfully submit that the cited references would not impart any reasonable expectation of success to one of ordinary skill in the art. At most, based on the general guidance of the cited references, coacervation of plasmid DNA with chitosan for enhancement of gene delivery was an approach seeming to be a promising field of experimentation. However, the cited references do not contain a sufficient teaching of how to obtain the desired result—an immune response based on nine RSV antigens. It is well settled that "obvious to try" is not the standard for obviousness under 35 U.S.C. §103. *Ex part Goldgaber*, 41 USPQ2d 1172, 1177 (B.P.A.I. 1996).

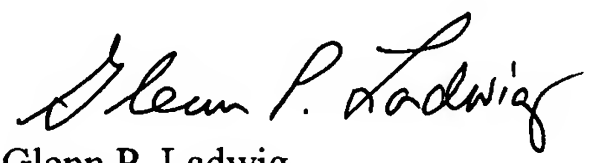
In view of the absence of a reasonable expectation of success in producing the immunogenic composition as currently claimed, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time
Request for Continued Examination under 37 C.F.R. §1.114
Information Disclosure Statement, with form PTO/SB/08 and copies of references